Timing of Corticosteroid Therapy Is Critical to Prevent Retinal Ganglion Cell Loss in Experimental Optic Neuritis

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PURPOSE. Acute vision loss from optic neuritis typically resolves; however, recovery is often not complete. Permanent vision loss from retinal ganglion cell (RGC) death occurs in 40% to 60% of patients. Current therapy (high-dose corticosteroids) speeds recovery but does not change final visual outcomes. Here the authors examined whether corticosteroids administered early in the disease course can prevent RGC loss in experimental optic neuritis.

METHODS. RGCs were retrogradely labeled with fluorogold in SJL/J mice. Experimental autoimmune encephalomyelitis (EAE) was induced by immunization with proteolipid protein peptide. Optic neuritis began 9 days after immunization. Mice were treated daily with dexamethasone, methylprednisolone, or PBS from days 0 to 14 or days 10 to 14 and then were killed on day 14, 18, or 22.

RESULTS. Corticosteroid treatment initiated before optic neuritis onset (days 0–14) suppressed EAE and reduced optic neuritis incidence through day 14. In the few eyes that developed optic neuritis, inflammation was mild, and RGC loss was attenuated. After treatment was stopped on day 14, mice rapidly developed EAE and optic neuritis by day 18, but RGC loss was still reduced. By day 22, RGC loss increased to levels similar to those of untreated optic neuritis eyes. Corticosteroid treatment after optic neuritis onset (days 10–14) slowed EAE progression and showed a trend toward suppression of optic neuritis and RGC loss on day 14 that was lost by day 18.

CONCLUSIONS. Corticosteroids can suppress optic neuritis and prevent RGC loss if treatment is initiated before optic nerve inflammation onset. Treatment is less effective after inflammation begins. Results suggest that chronic immunomodulation may prevent recurrent optic neuritis and RGC damage. (*Invest Ophthalmol Vis Sci.* 2010;51:1439–1445) DOI:10.1167/iops.09-4009

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Optic neuritis is an inflammatory demyelinating disease of the optic nerve that often occurs in patients with multiple sclerosis (MS).^{1–3} The disease is marked by acute loss of vision that often improves over several weeks as inflammation resolves; however, 40% to 60% of patients are left with some level of permanent vision loss.⁴ Permanent vision loss correlates with thinning of the retinal nerve fiber layer,^{5–7} suggesting that axonal damage of retinal ganglion cells (RGCs) is responsible for the vision loss.

The corticosteroid methylprednisolone is given intravenously, followed by oral prednisone, to some patients with acute optic neuritis.^{1,3,8} This treatment shortens the visual recovery period, but steroid treatment does not improve final visual acuity.^{1,3,8} These results suggest that steroids administered after optic neuritis onset can hasten the resolution of inflammation, but damage to RGC axons might already have been triggered and not reversed by steroid treatment.

Experimental autoimmune encephalomyelitis (EAE) is the most widely used model of MS and results in inflammation of the central nervous system, including optic nerve inflammation similar to optic neuritis.^{9,10} SJL/J mice immunized with proteolipid protein (PLP) develop relapsing-remitting EAE,⁹ resembling the most common disease course in MS patients.² Optic neuritis develops in approximately two-thirds of the eyes by day 11 after immunization in this model and leads to axonal injury and death of RGCs by day 14.^{11,12} Given that inflammation mediates RGC loss in experimental optic neuritis, we hypothesized that the suppression of inflammation with corticosteroids should prevent RGC damage. However, based on visual outcomes and nerve fiber layer changes seen in patients with optic neuritis, it is unclear whether this is true or whether there is a critical time necessary for administration of corticosteroids to have these effects. In the present study, EAE mice were treated systemically with two different corticosteroids (dexamethasone and methylprednisolone) both before and after optic nerve inflammation developed. RGC survival, incidence of optic neuritis, and EAE disease course were compared in order to determine whether corticosteroids have the potential to prevent RGC loss.

METHODS

Mice

Six-week-old female SJL mice were purchased from the Jackson Laboratory (Bar Harbor, ME). Treatment of the animals housed at the animal facilities at the University of the Pennsylvania and Thomas Jefferson University conformed to Institutional Animal Care and Use Committee guidelines and adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

FIGURE 1. Dexamethasone treatment beginning on the day of immunization suppresses EAE and optic neuritis and attenuates RGC loss. RGCs were retrogradely labeled by injection of fluorochrome into the superior colliculi of 7-week-old female SJL/J mice. Mice were immunized 1 week later (day 0) with PLP in CFA to induce EAE; controls were sham immunized with PBS in CFA. Mice were treated daily from days 0 to 14 with 200 mg/kg subcutaneous dexamethasone or an equal volume of PBS, then killed on day 14. (A) EAE mice treated with dexamethasone developed significantly less neurologic signs of EAE than mice treated with PBS alone. (B) The percentage of eyes that developed detectable optic nerve inflammation was lower in dexamethasone-treated EAE mice than in PBS-treated mice. (C) Longitudinal section through an optic nerve from a control mouse stained by hematoxylin and eosin demonstrates normal cellularity. (D) Optic nerve from 1 of 3 eyes from dexamethasone-treated EAE mice that did develop optic neuritis shows the relatively mild level of inflammation observed, with just a few small pockets of inflammatory cells (arrowheads) present. (E) Moderate to severe inflammation with numerous infiltrating cells within the optic nerve of a PBS-treated EAE mouse. (F) RGCs were photographed and counted in 12 standardized fields of flat-mounted retinas. Eyes with optic neuritis from PBS-treated mice had significantly fewer RGCs than eyes from control mice, eyes from EAE mice that did not develop optic neuritis, or the three eyes from dexamethasone-treated EAE mice that did develop optic neuritis (* $P < 0.0001$). Optic neuritis eyes from dexamethasone-treated mice had RGC numbers equivalent to those of control mice. Scale bars, 50 μ m (C-E).

RGC Labeling

Retrograde labeling of RGCs was performed as described previously.¹¹ Briefly, mice were anesthetized with 0.2 mL solution containing 10 mg/mL ketamine (Sigma, St. Louis, MO) and 1 mg/mL xylazine (Sigma), and a mediodorsal skin incision was made. Holes were drilled through the skull above each superior colliculus. Then 2.5 μ L of 1.25% hydroxystilbamidine (Fluorogold; Molecular Probes, Eugene, OR) in sterile water was injected stereotactically into each superior colliculus.

Induction and Evaluation of EAE

EAE was induced 1 week after RGC labeling, as described.¹¹ Briefly, the mice were anesthetized and injected subcutaneously with 0.1 mL solution containing 0.5 mg/mL proteolipid protein 139–151 (GenScript, Piscataway, NJ) emulsified in complete Freund's adjuvant (CFA; Difco, Detroit, MI) containing 2.5 mg/mL *Mycobacterium tuberculosis* (Difco) at two sites on the back. Control mice were injected with an equal volume of PBS and CFA. All mice were injected with 200 ng

pertussis toxin (List Biological, Campbell, CA) in 0.2 mL PBS intraperitoneally on day 0 (day of immunization) and again on day 2. Clinical EAE symptoms were scored daily on a 5-point scale as described previously¹³: 0, no disease; 0.5, partial tail paralysis; 1.0, tail paralysis or waddling gait; 1.5, partial tail paralysis and waddling gait; 2.0, tail paralysis and waddling gait; 2.5, partial limb paralysis; 3.0, paralysis of one limb; 3.5, paralysis of one limb and partial paralysis of another; 4.0, paralysis of two limbs; 4.5, moribund state; 5.0, death.

Corticosteroid Treatment

Dexamethasone (Sigma) treatment was administered once daily by subcutaneous injection at a concentration of 200 mg/kg in PBS. Methylprednisolone (Sigma) was injected intraperitoneally once daily at a concentration of 20, 40, or 80 mg/kg in PBS. Treatment with each corticosteroid was repeated daily from day 0 to day 14 or from day 10 to day 14 after immunization. Mice were killed on day 14, 18, or 22.

FIGURE 2. Withdrawal of dexamethasone treatment leads to a flare of EAE and optic neuritis. Control and EAE mice were treated daily from days 0 to 14 with 200 mg/kg dexamethasone or PBS, then continued to be observed daily after treatment was stopped until kill on day 18 or day 22. **(A)** Dexamethasone treatment significantly suppressed EAE through day 14 when mice were still being treated, but clinical EAE developed rapidly when treatment was discontinued after day 14, with disease severity equal to that found in PBS-treated EAE mice by day 16 and maintained through day 18. **(B)** The percentage of eyes with detectable optic nerve inflammation was no different 18 days after immunization between EAE mice treated with dexamethasone and those treated with PBS alone. **(C)** At day 18, the number of RGCs in optic neuritis eyes from PBS-treated EAE mice was significantly lower than in control eyes or optic neuritis eyes from dexamethasone-treated EAE mice ($P = 0.0018$). **(D)** At day 22, RGC numbers were significantly lower in optic neuritis eyes from both PBS- and dexamethasone-treated EAE mice than in eyes from control mice ($P = 0.0001$), but there was no significant difference between PBS-treated and dexamethasone-treated optic neuritis eyes.

Quantification of RGC Numbers

RGCs were viewed by fluorescence microscopy and counted as described previously.¹¹ Briefly, each eye was removed and fixed in 4% paraformaldehyde in PBS at the time of kill. The retina was removed from each eye, flat mounted, and viewed with a fluorescent microscope (Eclipse E600; Nikon, Tokyo, Japan). Photographs of labeled RGCs were taken at 20 $\times$ magnification in 12 standard fields—1/6, 3/6, and 5/6 of the retinal radius from the center of the retina in each quadrant. RGCs were counted in a masked fashion with imaging software (Image-Pro Plus 5.0; Media Cybernetics, Silver Spring, MD).

Histopathologic Evaluation of the Optic Nerves

Optic nerves were removed and fixed in 4% paraformaldehyde. Paraffin-embedded nerves were cut into 5- μ m longitudinal sections and stained with hematoxylin and eosin, and the presence of inflammatory cell infiltration was assessed by a masked investigator using a 4-point scale¹¹: 0, no infiltration; 1, mild cellular infiltration of the optic nerve or the optic nerve sheath; 2, moderate infiltration; 3, severe infiltration; 4, massive infiltration. The presence of optic neuritis was determined by any level of optic nerve inflammation (score 1–4), whereas nerves with no identifiable inflammation (score 0) were not considered to have optic neuritis. Each eye was analyzed individually because optic neuritis occurs as an independent event in this EAE model, with >40% of mice developing bilateral optic neuritis, >40% developing unilateral optic neuritis, and <20% developing no optic nerve inflammation.¹¹

Statistical Analysis

RGC numbers were compared between treatment groups by one-way ANOVA followed by Tukey's Multiple Comparison test using statistical software (GraphPad Prism 5.0; GraphPad Software, San Diego, CA). Data shown represent the mean $\pm$ SEM number of RGCs. Clinical EAE scores over time were compared between treatment groups by ANOVA for repeated measures using statistical software (GraphPad Prism 5.0; GraphPad Software), and Student's *t*-tests were used to

compared scores at single time points between treated and untreated mice. The number of eyes developing optic neuritis (no inflammation vs. any level of inflammation detected) and the relative level of inflammation (mild [score 1] vs. moderate to severe [score 2–4]) were compared with the two-tailed Fisher's exact test.

RESULTS

EAE and Optic Neuritis Suppression by Dexamethasone Treatment Beginning on Day of Immunization

Dexamethasone has been shown to markedly suppress EAE in rats.¹⁴ Therefore, we used an equivalent dose of dexamethasone to suppress EAE in SJL/J mice and to evaluate whether this immunosuppression also reduced optic nerve inflammation and RGC loss. Female SJL/J mice were immunized with PLP 1 week after RGC labeling to induce disease. The day of immunization was considered day 0. Control mice were sham-immunized with PBS. Mice were treated with 200 mg/kg dexamethasone by subcutaneous injection daily from day 0 through day 14 (the time of peak EAE disease and onset of significant RGC loss^{11,12}).

Dexamethasone treatment almost completely suppressed the development of clinical EAE through day 14 (Fig. 1A). Similarly, dexamethasone significantly reduced the incidence of optic neuritis detectable on histologic sections of optic nerves from mice killed on day 14 (Fig. 1B), with just 3 of 22 nerves from dexamethasone-treated mice containing inflammatory cell infiltrates compared with 12 of 22 nerves with inflammation from PBS-treated EAE mice ($P = 0.0039$). The degree of inflammation was also reduced (Figs. 1C–E), with all three optic neuritis nerves from dexamethasone-treated mice showing just mild inflammation (score, 1.0), whereas optic neuritis nerves from PBS-treated mice had an average inflammation

FIGURE 3. Methylprednisolone treatment beginning on the day of immunization suppresses EAE and reduces optic neuritis at higher doses. Control and EAE mice were treated daily from days 0 to 14 with 20 to 80 mg/kg intraperitoneal methylprednisolone or an equal volume of PBS, then killed on day 14. (A) 20 mg/kg methylprednisolone treatment significantly reduced signs of EAE compared with mice treated with PBS. (B) There was no significant difference in the percentage of eyes developing optic neuritis between PBS-treated and 20 mg/kg methylprednisolone-treated EAE mice. (C) Optic neuritis eyes from PBS-treated EAE mice had significantly fewer RGCs than control eyes ($P = 0.0175$), with a trend toward fewer RGCs than optic neuritis eyes from 20 mg/kg methylprednisolone-treated EAE mice that was not significant. (D) 40 mg/kg methylprednisolone treatment prevented RGC loss in optic neuritis eyes, with RGC numbers equivalent to those in control eyes. At 80 mg/kg, methylprednisolone almost completely blocked optic nerve inflammation, with just 1 of 12 eyes developing optic neuritis; that eye had normal RGC numbers.

score of 1.50 ± 0.52 (mean $\pm$ SD). In the few eyes that did develop optic neuritis with dexamethasone treatment, RGC survival was significantly increased compared with optic neuritis eyes from PBS-treated mice (Fig. 1F).

Development of EAE and Optic Neuritis after Withdrawal of Dexamethasone Treatment

EAE and control mice were treated daily with 200 mg/kg dexamethasone or PBS alone by subcutaneous injection from day 0 through day 14 after immunization. Mice were then killed on day 18, and optic nerves and retinas were removed. After treatment was stopped at day 14, mice rapidly developed EAE symptoms, with disease equivalent to that in PBS-treated EAE mice by day 18 (Fig. 2A). The incidence of optic neuritis also increased by day 18, close to levels in PBS-treated eyes (Fig. 2B), with 50% of nerves developing optic neuritis; at day 14, only 14% developed optic neuritis (Fig. 1B). The average level of inflammation was 1.25 ± 0.46 in dexamethasone-treated optic neuritis eyes compared with 1.30 ± 0.48 in PBS-treated optic neuritis eyes. Although the incidence of optic neuritis increased at day 18 in dexamethasone-treated mice, the treated eyes did not exhibit the significant RGC loss seen in PBS-treated optic neuritis eyes (Fig. 2C), with RGC numbers instead equivalent to those in control mouse eyes.

To determine whether the increased RGC survival at day 18 in EAE mice treated from days 0 to 14 with dexamethasone represents a lasting neuroprotective effect or rather indicates a delay in RGC loss because of the delayed onset of optic neu-

ritis, another cohort of control and EAE mice treated daily with 200 mg/kg dexamethasone or PBS from day 0 through day 14 was killed on day 22. Optic neuritis developed with similar incidence in PBS-treated eyes (57%; 8 of 14) and dexamethasone-treated eyes (50%; 6 of 12). Unlike day 18, significant RGC loss occurred in optic neuritis eyes from dexamethasone-treated EAE mice compared with control eyes, with similar RGC loss as seen in PBS-treated optic neuritis eyes (Fig. 2D).

EAE Suppression by Methylprednisolone Treatment Beginning on Day of Immunization

High-dose intravenous methylprednisolone treatment is given to some patients with optic neuritis to hasten visual recovery, though final visual outcome is not improved,^{1-3,8} suggesting that RGC survival may not be promoted by methylprednisolone initiated after optic neuritis onset. Paradoxically, earlier treatment in a rat chronic EAE model results in increased RGC apoptosis,¹⁵ but the effects of methylprednisolone in relapsing EAE are not known. We therefore treated relapsing EAE (in SJL/J mice immunized with PLP) daily from day 0 through day 14 with 20 mg/kg methylprednisolone by intraperitoneal injection, as used in previous studies.¹⁵ As did dexamethasone, methylprednisolone significantly suppressed the development of clinical EAE symptoms (Fig. 3A). However, though methylprednisolone did show a trend toward decreased incidence of optic neuritis compared with nerves from PBS-treated mice (Fig. 3B), this was not significant ($P = 0.3275$). The relative degree of optic nerve inflammation was 1.39 ± 0.87 in PBS-

treated mice and 1.13 ± 0.35 in methylprednisolone-treated mice. In the eyes of methylprednisolone-treated mice that did develop optic neuritis, there also was a trend toward increased RGC survival that was not significant ($P = 0.0818$) compared with optic neuritis eyes from PBS-treated EAE mice (Fig. 3C).

Although methylprednisolone treatment at 20 mg/kg showed a trend toward effects similar to those of dexamethasone in experimental optic neuritis, the effects were not significant, raising the question of whether methylprednisolone is inherently less effective, or whether the dose used, chosen based on its effectiveness in a rat chronic EAE model,¹⁵ is not maximally effective in this mouse model. To examine this, EAE mice were treated daily with 40 or 80 mg/kg methylprednisolone from day 0 through day 14 by intraperitoneal injection. This higher dosing suppressed EAE more effectively than 20 mg/kg methylprednisolone because none of the mice developed clinical signs of EAE ($n = 8/\text{group}$). The incidence of optic neuritis showed a trend toward reduction compared with PBS-treated EAE mice, with just 4 of 14 eyes (28.6%; $P = 0.0799$) developing optic neuritis in 40 mg/kg methylprednisolone-treated EAE mice. In 80 mg/kg methylprednisolone-treated EAE mice, the incidence was significantly reduced, with just 1 of 12 eyes (8.3%; $P = 0.0028$) developing optic neuritis. RGC loss was attenuated, with RGC numbers in 40 mg/kg methylprednisolone-treated optic neuritis eyes equivalent to those in control mouse eyes. The eye from 80 mg/kg methylprednisolone-treated mice that developed optic neuritis had RGC numbers within the range seen in control eyes (Fig. 3D). Although high-dose methylprednisolone did not demonstrate any toxic effects on RGC survival, cardiovascular side effects were observed. Mice became notably tachycardic immediately after treatment each day and required careful observation and frequent resuscitation. One mouse in the 40 mg/kg treatment group and two in the 80 mg/kg treatment died, apparently of these effects.

Corticosteroid Treatment after Disease Onset Slows EAE Progression without Preventing RGC Loss

Although early treatment with dexamethasone exhibits significant ability to suppress optic neuritis and RGC loss, patients do not seek treatment for the initial episode of optic neuritis until after inflammation begins. The potential for corticosteroids to reduce RGC loss when administered after onset of experimental optic neuritis was therefore evaluated. In relapsing EAE, we have shown that optic nerve inflammation begins by day 9 after immunization.^{11,12} Here, RGCs were labeled, and 1 week later SJL/J mice were immunized with PLP (day 0). Control and EAE mice were then treated with 200 mg/kg dexamethasone or PBS alone by subcutaneous injection daily from day 10 through day 14. In parallel experiments mice were treated with 20 mg/kg methylprednisolone or PBS by intraperitoneal injection daily from day 10 through day 14. Mice were killed on either day 14 or day 18, and optic nerve inflammation and RGC numbers were compared.

Dexamethasone treatment suppressed EAE progression, with little progression of disease after treatment initiation and no spike in disease symptoms after the withdrawal of treatment (Fig. 4A). Suppression was significant over time by repeated-measures ANOVA ($P = 0.0304$), though there was no significant EAE reduction on any single day. Methylprednisolone similarly halted the progression of EAE, with significant suppression of symptoms during the peak of disease at days 12 to 14 (Fig. 4B). EAE did not spike after treatment stopped, but suppression of disease was no longer significant during the typical early recovery phase through day 18.

Unlike early treatment by which dexamethasone significantly reduced the incidence of optic nerve inflammation (Fig.

FIGURE 4. Corticosteroid treatment beginning after disease onset slows the progression of EAE. (A) Mice immunized with PLP on day 0 were treated daily with 200 mg/kg dexamethasone or an equal volume of PBS from days 10 to 14 and were observed daily through day 18 for signs of EAE. Typical early signs of EAE were observed by days 9 to 10. After treatment was initiated, EAE severity was significantly reduced in dexamethasone-treated mice compared with PBS-treated mice ($P = 0.0304$ for repeated measures). (B) Mice immunized with PLP on day 0 were treated daily with 20 mg/kg methylprednisolone or an equal volume of PBS from days 10 to 14 and observed daily through day 18 for signs of EAE. Typical early signs of EAE were observed by days 9 to 10. Methylprednisolone significantly suppressed the peak of EAE disease on days 12 to 14.

1B), dexamethasone treatment from days 10 to 14 showed only a nonsignificant ($P = 0.2377$) trend toward decreased optic neuritis incidence on day 14 (Fig. 5A), with a similar degree of inflammation observed in eyes that did develop optic neuritis between dexamethasone-treated (1.25 ± 0.50) and PBS-treated (1.28 ± 0.48) EAE mice; no decrease in optic neuritis was observed at day 18 ($P = 0.5108$; Fig. 5B). Methylprednisolone treatment from days 10 to 14 also failed to reduce the incidence and degree of optic neuritis at day 14 ($P = 0.7638$; Fig. 5C) and day 18 ($P = 1.000$; Fig. 5D). Among those eyes that developed optic neuritis, neither dexamethasone treatment nor methylprednisolone treatment (Fig. 6) resulted in a significant increase in RGC survival compared with PBS treatment of EAE mice.

DISCUSSION

Early treatment with corticosteroids, beginning before detectable optic nerve inflammation, significantly suppressed the development of experimental optic neuritis and preserved RGCs in the relapsing/remitting model of MS in these studies. These results demonstrate that immunosuppression does have the potential to prevent neuronal injury from inflammatory demyelinating disease of the central nervous system if treatment can be initiated early enough. Although treatment obvi-

FIGURE 5. Corticosteroid treatment beginning after disease onset does not suppress optic neuritis. (A) Dexamethasone treatment daily from days 10 to 14 led to a trend toward decreased incidence of optic neuritis at day 14 in EAE mice compared with PBS treatment. This effect was not significant ($P = 0.2377$). (B) No difference in optic neuritis incidence was found at day 18 between EAE mice treated daily from days 10 to 14 with dexamethasone compared with PBS. (C, D) Similarly, no difference in optic neuritis incidence was found at day 14 (C) or day 18 (D) between EAE mice treated daily from days 10 to 14 with methylprednisolone compared with PBS.

ously cannot be initiated in patients before their clinical presentation, our results suggest that patients who are at risk for recurrent episodes of optic neuritis, as occurs in many MS patients, may indeed benefit from the neuroprotective effects of chronic immunosuppressive therapy, even though currently used immunomodulatory therapies for MS have shown only limited ability to reduce neurologic disability.^{16,17} Although early corticosteroid treatment significantly reduced RGC loss, the withdrawal of treatment resulted in the rapid development of EAE and optic neuritis, suggesting that continuous active immunosuppression likely is needed to prevent the disease.

Both the dose of treatment used and the specific underlying disease process likely play important roles in response to corticosteroid treatment for optic neuritis. Although methylprednisolone showed little neuroprotective benefit in this relapsing disease model at 20 mg/kg, higher doses did show suppression of optic neuritis and RGC loss with early treatment, similar to results with dexamethasone. There was no evidence of worsening of neuronal injury when treatment was administered before or after disease onset. In a model of chronic EAE, however, early treatment with methylprednisolone before nerve inflammation actually led to increased loss of RGCs by

FIGURE 6. RGC loss is not attenuated by dexamethasone or methylprednisolone when treatment begins after disease onset. RGCs were labeled with fluorochrome, and mice were immunized 1 week later (day 0) with PLP in CFA to induce EAE, or controls were sham immunized with PBS in CFA. Mice were treated daily from days 10 to 14 with 200 mg/kg dexamethasone, 20 mg/kg methylprednisolone, or an equal volume of PBS. Mice were killed on day 14 or day 18, and RGCs were counted by fluorescence microscopy. (A) 14 days after immunization, significant loss of RGCs was detected in eyes with optic neuritis compared with control mouse eyes in all treatment groups ($*P < 0.05$). (B) 18 days after immunization, significant loss of RGCs was detected in eyes with optic neuritis compared with control mouse eyes in the PBS and dexamethasone treatment groups ($*P < 0.05$), with a similar trend toward decreased RGC numbers in optic neuritis eyes from methylprednisolone-treated EAE mice.

suppressing an endogenous neuroprotective pathway.¹⁵ This model of chronic EAE, clinically similar to primary progressive MS, induces a distinct course of optic neuritis, with significant RGC loss occurring before detectable optic nerve inflammation^{18,19} as opposed to the axonal damage and RGC loss in the relapsing disease model, which is detectable only several days after optic nerve inflammation.¹² The different time courses of RGC damage and responses to therapy in some ways recapitulate clinical findings in central nervous system demyelinating disease in which small residual neurologic deficits from neuronal loss can accumulate after acute episodes in relapsing/remitting disease.² Progressive demyelinating disease, on the other hand, undergoes a slow neurologic decline without remission, felt to be caused more by neurodegeneration than inflammation, and shows less response to common immunomodulatory therapies.^{20–22} Comparative studies of immunomodulatory and neuroprotective therapies between these two models will be useful for identifying underlying common and disease-specific mechanisms.

Together, the current studies suggest that immunosuppressive therapy does have the potential to reduce neurodegenerative aspects of central nervous system demyelinating disease, but the specific nature of the inciting degenerative process and the timing of therapy will be critical to the development of any successful therapy. Chronic immunomodulatory therapy has the potential to prevent cumulative loss of RGCs and subsequent loss of vision in MS patients or others at high risk for recurrent episodes of optic neuritis.

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